

# Gut Microbiota and the Alteration of Immune Balance in Skin Diseases: From Nutraceuticals to Fecal Transplantation

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## Abstract

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The P.N.E.I. (Psycho-Neuro-Endocrine-Immunology) approach is represented by the interdisciplinary concept of bidirectional cross-talk between the psycho-neuro-endocrine and immune systems, which can influence the immune response. The well-known Gut-Brain Axis and the Gut-Skin Axis can be merged in a bigger network- the Gut-Brain-Skin Axis, with complex regulation by cytokines, neuro-peptides, neuro-hormones and another messenger (signalling) molecules and maybe the most important modulator of the Gut-Brain-Skin Axis/ the gut microbiota. The role of gut bacterial homeostasis is very important, and the homeostatic imbalance of the immune response may be a relevant etiologic/pathophysiologic factor for extra-intestinal and intestinal inflammatory, allergic and autoimmune diseases. The Low Dose Cytokines Medicine (LDM) is an innovative therapeutic approach. It is based on the most advanced knowledge in molecular biology and low dose pharmacology with the primary outcome. The SKA (Sequential Kinetic Activation) technology, codified and standardised by GUNA S.p.a. -Italy- makes the low doses of signalling molecules able to be active even below the minimum dose classically considered as effective and the significative efficacy of orally administered low-dose signalling molecules is the most representative aspect of LDM. The Physiologic Nutraceuticals and the Low Dose Medicine are two of the most promising approaches for the treatment of skin diseases based on the rebalance of the immune response and the recovery of gut dysbiosis.

## Introduction

The P.N.E.I. (Psycho-Neuro-Endocrine-Immunology) approach is represented by the interdisciplinary concept of bidirectional cross-talk between the psycho-neuro-endocrine and immune systems, which can influence the immune response. Also, the immune system can influence the neuroendocrine functions, and this very complex interplay is mediated by a network of a lot of different

hormones, neuropeptides, growth factors, cytokines and other signalling molecules [1], [2], [3].

Skin and gut roles and relations with other organs and tissues are examples of the P.N.E.I. functioning. They are complex immune and neuroendocrine organs integrated into the whole immune-endocrine systems and the most important contact organs of all animals with the environment, with a lot of common characteristics: colonized by specific microbial strains, with a large number of vascular and neural structures, constantly exposed to

a heavy antigenic charge, represented by bacterial flora, with the tolerance of the commensal microbiota. The well-known Gut-Brain Axis and the Gut-Skin Axis can be merged in a larger network-the Gut-Brain-Skin Axis, with complex regulation by cytokines, neuropeptides, neuro-hormones and other messenger (signaling) molecules and maybe the most important modulator of the Gut-Brain-Skin Axis/the gut microbiota [2], [3], [4], [5].

## Gut microbiota

It is well known that the gastrointestinal tract is colonised by about 100 trillion bacterial population (microbiota) composed of non-commensal (pathogenic) and commensal (nonpathogenic) species. Microbiota differs in composition and also in the function based on numerous factors such as the specific GI segment but also the diet of a subject, the gender, the age, etc. The nucleus of 57 species is common to all individuals, but each human being has a specific and unique microbiota. The dominant bacterial *fila*, constituting over 90% of the species present in the human intestine, are *Bacteroides* and *Firmicutes*, but also *Lactobacilli*, *Bacteroides*, *Proteobacteria*, *Bifidobacteria* and *Streptococci* are common [3], [4], [5], [6], [7].

The role of gut bacterial homeostasis is very important, and the homeostatic imbalance of the immune response may be a relevant etiologic factor for extra-intestinal and intestinal inflammatory, allergic and autoimmune diseases. This role is not limited to its systems but the whole organism [1], [4], [8].

Gram-negative bacteria, which contain lipopolysaccharide are considered as the main proinflammatory strains, responsible for the expression of pro-inflammatory cytokines such as Interleukin-1 (IL-1) and Interleukin-6 (IL-6) [2], [9].

Formation of biofilm is identified as one of the main forms of chronic intestinal, an adherent conglomerate to the intestinal epithelium having a composition like the extracellular matrix, in which bacteria and fungi proliferate and resid. The antibiotic treatment can affect mostly the bacterial infection caused by bacteria external to the biofilm, and an immune response is not able to be fully effective on biofilm. So, biofilm could be one of the most important etiologic agents of numerous chronic inflammatory diseases, promote the persistence of a Low-Grade Chronic Inflammation (LGCI) that can lead to the Leaky Gut Syndrome, connected with the onset of autoimmune and allergic diseases [1], [10], [11], [12], [13].

The physiological inflammation is supported by Th1-related cytokines-IL-1, TNF- $\alpha$  and IL-6 and these cytokines induce the production of other pro-

inflammatory agents-adhesive molecules, chemokines, growth factors and other mediators such as prostaglandins and nitric oxide (NO) with the stimulation of the leukocyte at the site of inflammation. IL-6 acts as the secondary mediator, responsible for maintaining the inflammatory response itself. Inflammation leads to the increasing level of Interleukin-10 (IL-10), which is the most important Th2 anti-inflammatory cytokine involved in the inflammation resolution phenomenon [3], [4], [12], [13], [14].

LGCI also has systemic effects, and it is often responsible for the disruption of skin immune homeostasis and systemic diseases such as obesity, Type II Diabetes, Vitiligo, Atopic Dermatitis, Psoriasis, BPCO (Broncho-Pulmonary-Chronic-Obstructive Pulmonary Disease) or the RRI (Recurrent Respiratory Infections), Rheumatoid Arthritis, etc.

The key risk factor for the development of allergic sensitisation is the perturbation of microbiota development during the first years of life (due to maternal consumption of antimicrobials during pregnancy, formula feeding or antimicrobial exposure or caesarean birth) [15], [16], [17].

The presence of a shift ("Th1/Th2 shift") of the immunological balance as a consequence of an imbalance between the cytokines expressed by Th1/Th17 and T<sub>reg</sub>/Th2 lymphocyte subpopulations is one of the most important etiologic factors for a large number of dermatologic diseases. Th1 cytokines hyper-production is strictly linked with inflammatory and autoimmune skin diseases such as Psoriasis and Vitiligo, with the central role of a class of memory T-cells characterised by the presence of the Cutaneous Lymphocyte Antigen (CLA) on their surface and responsible for skin-homing T cell.

The presence of systemic LGCI is a strong trigger for CLA<sup>+</sup> T-cells [17], [18], [19], [20].

As two of the most important etiologic factors for many of chronic dermatologic inflammatory, autoimmune and allergic diseases, gut dysbiosis (biofilm) and LGCI are currently considered therapeutic targets, but there are no standard therapeutic opportunities to treat LGCI. Also, and very important is that the chronic use of active anti-inflammatory molecules designed for the treatment of acute inflammatory phenomena shows an unfavourable efficacy/adverse effects ratio. Anti-cytokine therapy was proposed for the treatment of inflammatory and autoimmune diseases. The need of high doses of active molecules to reach the therapeutic goal and the low compliance of systemic administration performed by injective routes are the most important and limiting pitfalls connected with the use of high dosage cytokines and other signal molecules [21], [22], [23].

The Low Dose Cytokines Medicine (LDM) is an innovative therapeutic approach. It is based on the

most advanced knowledge in molecular biology and low dose pharmacology with the primary outcome.

The SKA (Sequential Kinetic Activation) technology, codified and standardised by GUNA S.p.a. -Italy- makes the low doses of signalling molecules able to be active even below the minimum dose classically considered as effective and the significative efficacy of orally administered low-dose signalling molecules is the most representative aspect of LDM [17], [22], [23], [24].

The SKA of low dose signalling molecules activates some units of cellular (or plasmatic) receptors by their low concentration.

The researchers performed a double-blind multicenter versus placebo clinical study was conducted on a dermatologic disease in 2014 for treating patients with Psoriasis Vulgaris in order to test the LDM approach with the oral administration of low dose SKA activated cytokines with the great effectiveness of the treatment assessing improvement of the psoriatic lesions and of quality of life (PASI (Psoriasis Area Severity Index) and ii) DLQI (Dermatology Life Quality Index). This study showed the effectiveness and the safety of the SKA low dose cytokines treatment and also that the SKA low dose cytokines treatment has a long action term, which extends over the months following the end of treatment [25], [26], [27], [28].

Lotti T. and colleagues, in 2015, were organised a retrospective clinical study and the effectiveness of adopted treatments for Vitiligo were compared and analysed the clinical data collected from patients who received different treatments for Vitiligo. Patients were treated with low-dose SKA IL-10, IL-4; b-FGF and anti-IL-1 antibodies, topical treatments with cortisone cream alone or in association with both groups of low dose molecules and nbUVB radiation alone or in association with both groups of molecules low dose. Other patients were treated with oral intake of extracts from Ginkgo biloba and with exposure to natural sunlight

The treatment with low dose SKA b-FGF registered an improvement in 74% of the patients. The combination of low doses SKA IL-4, IL-10 and anti-IL-1 antibodies registered an improvement in 77% of patients. The greatest improvement was registered with the association of treatments with low dose SKA molecules and UV-B treatment which has led to improvements in 92/93. No adverse effects have been reported, and the safety and efficacy of low dose SKA were verified [29], [30], [31]. The randomised, double-blinded, controlled clinical trial included children with mild to medium IgE-mediated and non-IgE mediated Atopic Dermatitis in an acute phase of the disease was conducted using low dose SKA (IL-12 and IFN- $\gamma$ ). The main outcome was the reduction of the AD quantified as a reduction of SCORAD index of at least 30%; in the same group, the decrease of SCORAD value continues during the follow-up period reaching

64%. The treated group showed a significant reduction of the intake of drugs for symptoms control (antihistamines and topical corticosteroids) with progressive improvement of the quality of life. No adverse effects have been reported [32], [33], [34].

## Conclusions

The disruption of gut and skin homeostatic equilibrium has not only local but also systemic negative outcomes. Gut dysbiosis and inflammatory phenomena are one of the most important etiological components of many dermatologic diseases.

A rebalance action of the gut microbiota and a rebalancing of the inflammatory immune response, for the treatment of many diseases, not adequately managed with currently available therapies, are needed.

The study of biofilm formation and consolidation dynamics and the search for substances, of both natural and synthetic origin, able to intervene effectively on them, could be extremely useful.

It is now possible to design an effective treatment protocol for dysbiosis using medical devices and food supplements, also useful to prevent both dysbiosis and biofilm formation. In selected cases, faecal transplantation is needed.

The availability of Low Dose SKA signalling molecule is the most important point of LDM. Oral administration of low dose SKA signalling molecules represents the innovative core of the entire strategy for the treatment of dermatological diseases characterised by an immune imbalance and LGCI such as in Psoriasis Vulgaris, Vitiligo and Atopic Dermatitis.

The Physiologic Nutraceuticals and the Low Dose Cytokines Medicine and faecal transplantation two of the most promising approaches for the treatment of skin diseases based on the rebalance of the immune response and the recovery of gut dysbiosis.

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